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Measles vaccine: a 27-year follow-up

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SUMMARY

In 1964, the Medical Research Council undertook a trial of measles vaccine in over 36000 United Kingdom children; 9577 of whom received live vaccine, 10625 received inactivated followed by live vaccines, and 16328 acted as unvaccinated controls. Participants in this study have been followed to determine the long term protection from measles vaccine and follow-up data were available on 4194, 4638 and 274 respectively. During the 5-year period 1986–90, the protective efficacy of live measles vaccine has remained high at 87%, but the 95% confidence interval was wide (−43 to 99%) due to the small numbers of cases. Between 1976 and 1990, however, the overall efficacy of the live vaccine was 92% (95% confidence interval 86 to 95%) and there was no evidence of a decline in efficacy ($P = 0{\cdot}13$) over the 15-year period. This study suggests that the protection from live measles vaccine persists for up to 27 years after vaccination, and that no change in the current United Kingdom measles immunization policy should be made on the grounds of waning immunity.

INTRODUCTION

Live attenuated measles vaccine was introduced into the United Kingdom immunization schedule in 1968. This was replaced by a combined measles, mumps, rubella (MMR) vaccine in 1988 and, currently, only one dose of MMR is given between the ages of 12 months and 2 years [1].

In the USA, where MMR vaccine has been used since 1972, an increase in measles cases, particularly amongst older children and adolescents, led to a change in policy [2]. Since 1989, most children in the United States have been scheduled to receive a first dose of MMR vaccine at 15 months followed by a second dose either at or after school entry. Two-dose schedules of MMR vaccination are also used in other countries including Sweden and Finland [3]. A recent increase in cases reported amongst older children has prompted a call for a two-dose schedule to also be adopted in the United Kingdom [4–6].

There are many possible reasons for an observed increase in cases amongst older children [2–6]. One reason, which would indicate that a second dose of measles

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vaccine may be necessary, is that these cases represent vaccine failures [3–6]. Primary vaccine failure occurs when an individual fails to develop an adequate immune response to the initial vaccination. Secondary vaccine failure occurs when protection is initially adequate but immunity is lost over time [2]. To determine whether waning of immunity is a significant problem in the United Kingdom, data on the long-term protection provided by measles vaccine are needed.

In the United Kingdom, the long-term protection afforded by live measles vaccine was last assessed in 1987 [8]. The cohort used were participants remaining from the Medical Research Council trial who received measles vaccine in 1964 and has been followed for up to 21 years [8–12]. In this paper, data from the further follow up of this cohort, up to 1990, have been reviewed, 27 years after the initial vaccination.

METHODS

In 1964, 36530 children aged between 10 months and 2 years and without a history of clinical measles were allocated to one of three groups. One group (9577 children) received a Schwartz strain of live measles vaccine, the second group (10625 children) received the same vaccine but 4 weeks after a dose of inactivated vaccine, and the third group (16238 children) remained unvaccinated. Due to the subsequent withdrawal of five participating local authorities to take part in another study, approximately 2000 children were lost from each of the study groups after the first 9 months [10]. In addition many children, particularly amongst the unvaccinated group, developed measles or were offered vaccine as part of the national scheme. Therefore, in 1969, the unvaccinated group was extended to include those who had defaulted or who had been ineligible for vaccination [10]. This was judged valid because the measles attack rate in these unvaccinated groups had been similar to that in the true controls [10].

Follow up

Since 1965, an annual postal survey has been carried out, which requested details of the occurrence of, or contact with, a case of measles. Non-responders received two further reminders each year, and participants were excluded from further follow up because of death, when no reply was received for 3 successive years, or when measles was reported. By the end of 1990, there remained in the study 4194 live measles vaccine recipients, 4638 who had received both inactivated and live vaccines, and 274 unvaccinated participants.

For each person who reported a case of measles, confirmation was sought from the general practitioner, and only cases confirmed in this manner are included in the analysis of vaccine efficacy. Estimates of vaccine efficacy and confidence intervals were obtained using Poisson regression of the rate of measles in the vaccinated and unvaccinated groups.

RESULTS

Between 1985 and 1990 the annual response rate has remained high, with a mean of 93% for those in the live and the inactivated/live vaccine groups, and 87% in the unvaccinated group. The incidence of physician-confirmed measles has

Table 1. *Protective efficacy of measles vaccine per 5-year period 1976–90*

	Live vaccine			Inactivated/live vaccine*			Unvaccinated	
Period	Number of cases	Attack rate/ 100 person years	Protective efficacy (95% confidence interval)	Number of cases	Attack rate/ 1000 person years	Protective efficacy (95% confidence interval)	Number of cases	Attack rate/ 1000 person years
1976–80	17	0·681	94 (88–97)	20	0·776	93 (87–96)	23	10·9
1981–5	8	0·342	72 (−34–94)	24	0·979	19 (−244–81)	2	1·20
1986–90	2	0·097	87 (−43–99)	2	0·093	88 (−36–99)	1	0·75
1976–90	27	0·227	92 (86–95)	46	0·565	86 (78–92)	26	1·00

* Inactivated vaccine followed by live vaccine after 4 weeks.

continued to fall since 1985 in line with national trends. An increase in 1988 corresponded to an increase in notifications in England and Wales.

The attack rates and estimated efficacy for 5-yearly periods between 1976 and 1990 are shown in Table 1. During 1986–90, estimated efficacy against measles in the live and inactivated/live vaccine groups remained high (87% and 88% respectively) but confidence intervals were wide due to small numbers of cases. Over the 15-year period 1976–90, there was no evidence of a trend in the efficacy of live measles vaccine with time ($P = 0{\cdot}13$), but there was evidence of a downward trend in the inactivated/live group ($P = 0{\cdot}02$).

DISCUSSION

In line with national trends [13], the incidence of measles in our study population has continued to fall, with only five cases having been reported in the study population between 1986 and 1990. Our study suggests that the efficacy of live measles vaccine remains high 27 years after vaccination and that there has been no marked decline in this protection over the past 15 years. The decline observed in the inactivated/live vaccine group is of historical interest only as this schedule has not been used in the United Kingdom since 1968 [12].

In contrast, evidence has been presented from the USA of the waning of protection following live measles vaccine. During a measles outbreak amongst vaccinated college students, the attack rate was shown to increase with time since vaccination [14], but as efficacy estimates could not be obtained, the magnitude of the fall in protection could not be determined. Until recent years in the United Kingdom, unlike the USA, measles has remained endemic, and the participants in our study are likely to have been exposed to natural infection [8]. High levels of measles antibody have been demonstrated in asymptomatic vaccinated school-children during the course of a measles outbreak [15], suggesting that the boosting of antibody levels by exposure to natural infection may occur. Therefore, boosting by such exposure in the United Kingdom could have extended the duration of

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apparent protection observed in our study. A study from China, however, where reported measles morbidity was kept at a very low level, also demonstrated that protection from measles vaccine may persist for 15 years [16]. This supports the observation in this paper that significant waning of immunity does not occur.

In view of the low incidence of measles in this study, further precise estimates of the long term protection afforded by measles vaccine will not be obtained. On present evidence, however, secondary vaccine failures are not likely to be a major public health problem in the United Kingdom. Future changes in measles vaccine policy may be required for a number of reasons, for example to improve coverage or to revaccinate primary vaccine failures. This study does not support the need for a change in policy on the basis of waning immunity.

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